Amendments to the Specification:

Please replace the paragraph beginning at page 10, line 28, with the following rewritten paragraph:

-- In an embodiment, of the invention the cleavage recognition site is the cleavage recognition site for a cancer-associated protease. In particular embodiments, the linker amino acid sequence comprises SLLKSRMVPNFN (SEQ ID NO: 40) or SLLIARRMPNFN (SEQ ID NO: 90) cleaved by cathepsin B; SKLVQASASGVN (SEQ ID NO: 45) or SSYLKASDAPDN (SEQ ID NO: 46) cleaved by an Epstein-Barr virus protease; RPKPQQFFGLMN (SEQ ID NO: 41) cleaved by MMP-3 (stromelysin); SLRPLALWRSFN (SEQ ID NO: 42) cleaved by MMP-7 (matrilysin); SPQGIAGQRNFN (SEQ ID NO: 43) cleaved by MMP-9; DVDERDVRGFASFL (SEQ ID NO: 44) cleaved by a thermolysin-like MMP; SLPLGLWAPNFN (SEQ ID NO: 87) cleaved by matrix metalloproteinase 2(MMP-2); SLLIFRSWANFN (SEQ ID NO: 93) cleaved by cathespin L; SGVVIATVIVIT (SEQ ID NO: 96) cleaved by cathespin D; SLGPQGIWGQFN (SEQ ID NO: 99) cleaved by matrix metalloproteinase 1(MMP-1); KKSPGRVVGGSV (SEQ ID NO: 102) cleaved by urokinase-type plasminogen activator; PQGLLGAPGILG (SEQ ID NO: 105) cleaved by membrane type 1 matrixmetalloproteinase (MT-MMP); HGPEGLRVGFYESDVMGRGHARLVHVEEPHT (SEQ ID NO: 108) cleaved by stromelysin 3 (or MMP-11), thermolysin, fibroblast collagenase and stromelysin-1; GPQGLAGQRGIV (SEQ ID NO: 111) cleaved by matrix metalloproteinase 13 (collagenase-3); GGSGQRGRKALE (SEQ ID NO: 114) cleaved by tissue-type plasminogen activator(tPA); SLSALLSSDIFN (SEQ ID NO: 117) cleaved by human prostate-specific antigen; SLPRFKIIGGFN (SEQ ID NO: 120) cleaved by kallikrein (hK3); SLLGIAVPGNFN (SEQ ID NO: 123) cleaved by neutrophil elastase; and FFKNIVTPRTPP (SEQ ID NO: 126) cleaved by calpain (calcium activated neutral protease). The nucleic acid sequences for ricin A and B chains with each of the linker sequences are shown in Figures 2D, 35C, 3D, 4D, 5D, 6D, 16D, 17D, 34C, 36C, 37C, 38C, 39C, 40C, 41C, 42C, 43C, 44C, 45C, 46C and 47C, respectively.--

Please replace the paragraph beginning at page 11, line 19, with the following rewritten paragraph:

--In another embodiment, the cleavage recognition site is the cleavage recognition site for a protease associated with the malaria parasite, *Plasmodium falciparum*. In particular embodiments, the linker amino acid sequence comprises QVVQLQNYDEED (SEQ ID NO: 55); LPIFGESEDNDE (SEQ ID NO: 56); QVVTGEAISVTM (SEQ ID NO: 57); ALERTFLSFPTN (SEQ ID NO: 58) or KFQDMLNISQHQ (SEQ ID NO: 59). The nucleic nucleotide sequences for ricin A and B chains with each of the linker sequences are shown in Figures 7D, 8D, 9D, 10D, and 11D.--

Please replace the paragraph beginning at page 11, line 26, with the following rewritten paragraph:

--In a another embodiment, the cleavage recognition site is the cleavage recognition site for a viral protease. The linker sequences preferably comprise the sequence Y-X-Y-A-Z wherein X is valine or leucine, Y is a polar amino acid, and Z is serine, asparagine or valine. In particular embodiments, the linker amino acid sequence comprises SGVVNASCRLAN (SEQ ID NO:63) or SSYVKASVSPEN (SEQ ID NO:64) cleaved by a human cytomegalovirus protease; SALVNASSAHVN (SEQ ID NO:60) or STYLQASEKFKN (SEQ ID NO:61) cleaved by a herpes simplex 1 virus protease; SSILNASVPNFN (SEQ ID NO:62) cleaved by a human herpes virus 6 protease; SQDVNAVEASSN (SEQ ID NO:65) or SVYLQASTGYGN (SEQ ID NO:66) cleaved by a varicella zoster virus protease; or SKYLQANEVITN (SEQ ID NO:67) cleaved by an infectious laryngotracheitis virus protease. The nucleic nucleotide sequences for ricin A and B chains with each of the linker sequences are shown in Figures 12D, 13D, 14D, 15D, 18D, 19D, 20D, and 22D.--

Please replace the paragraph beginning at page 12, line 5, with the following rewritten paragraph:

--In another embodiment, the cleavage recognition site is the cleavage recognition site for a hepatitis A viral protease. In particular embodiments, the linker

amino acid sequence comprises SELRTQSFSNWN (SEQ ID NO.68) or SELWSQGIDDDN (SEQ ID NO.69) cleaved by a hepatitis A virus protease. The nucleic nucleotide sequences for ricin A and B chains with each of the linker sequences are shown in Figures 23D or 24D. --

Please replace the paragraph beginning at page 12, line 5, with the following rewritten paragraph:

--In another embodiment, the cleavage recognition site is the cleavage recognition site for a hepatitis C viral protease. In particular embodiments, the linker amino acid sequence comprises DLEVVTSTWVFN (SEQ ID NO.75), DEMEECASHLFN (SEQ ID NO.78), EDVVCCSMSYFN (SEQ ID NO.81) or KGWRLLAPITAY (SEQ ID NO.84) cleaved by a hepatitis C virus protease. The nucleic nucleotide sequences for ricin A and B chains with each of the linker sequences are shown in Figures 30C, 31C, 32C and 33C.--

Please replace the paragraph beginning at page 12, line 5, with the following rewritten paragraph:

--In another embodiment, the cleavage recognition site is the cleavage recognition site for a *Candida* fungal protease. In particular embodiments, the linker amino acid sequence is SKPAKFFRLNFN (SEQ ID NO.70), SKPIEFFRLNFN (SEQ ID NO.71) or SKPAEFFALNFN (SEQ ID NO.72) cleaved by *Candida* aspartic protease. The nucleic nucleotide sequences for ricin A and B chains with the first linker sequence are shown in Figures 25D.--

Please replace the paragraphs beginning at page 15, line 21 to page 25, line 12, with the following rewritten paragraphs:

--Figure 1 shows the DNA sequence of the baculovirus transfer vector, pVL1393 (SEQ ID NO.1);

Figure 2A summarizes the cloning strategy used to generate the pAP-213 construct (SEQ ID NO.2);

Figure 2B shows the nucleotide sequence of the Cathepsin B linker regions of pAP-213;

Figure 2C shows the subcloning of the Cathepsin B linker variant into a baculovirus transfer vector;

Figure 2D shows the DNA sequence of the pAP-214 insert containing ricin and the Cathepsin B linker (SEQ ID NO.3);

Figure 3A summarizes the cloning strategy used to generate the pAP-215 construct;

Figure 3B shows the nucleotide sequence of the MMP-3 linker regions of pAP-215 (SEQ ID NO.4);

Figure 3C shows the subcloning of the MMP-3 linker variant into a baculovirus transfer vector;

Figure 3D shows the DNA sequence of the pAP-216 insert containing ricin and the MMP-3 linker (SEQ ID NO.5);

Figure 4A summarizes the cloning strategy used to generate the pAP-217 construct;

Figure 4B shows the nucleotide sequence of the MMP-7 linker regions of pAP-217 (SEQ ID NO.6);

Figure 4C shows the subcloning of the MMP-7 linker variant into a baculovirus transfer vector;

Figure 4D shows the DNA sequence of the pAP-218 insert containing ricin and the MMP-7 linker (SEQ ID NO.7);

Figure 5A summarizes the cloning strategy used to generate the pAP-219 construct;

Figure 5B shows the nucleotide sequence of the MMP-9 linker regions of pAP-219 (SEQ ID NO.8);

Figure 5C shows the subcloning of the MMP-9 linker variant into a baculovirus transfer vector;

Figure 5D shows the DNA sequence of the pAP-220 insert containing ricin and the MMP-9 linker (SEQ ID NO.9);

Figure 6A summarizes the cloning strategy used to generate the pAP-221 construct;

Figure 6B shows the nucleotide sequence of the thermolysin-like MMP linker regions of pAP-221 (SEQ ID NO.10);

Figure 6C shows the subcloning of the thermolysin-like MMP linker variant into a baculovirus transfer vector.

Figure 6D shows the DNA sequence of the pAP-222 insert containing ricin and the thermolysin-like MMP linker (SEQ ID NO.11);

Figure 7A summarizes the cloning strategy used to generate the pAP-223 construct;

Figure 7B shows the nucleotide sequence of the Plasmodium falciparum-A linker regions of pAP-223 (SEQ ID NO.12);

Figure 7C shows the subcloning of the Plasmodium falciparum-A linker variant into a baculovirus transfer vector;

Figure 7D shows the DNA sequence of the pAP-224 insert containing ricin and the Plasmodium falciparum-A linker (SEQ ID NO.13);

Figure 8A summarizes the cloning strategy used to generate the pAP-225 construct;

Figure 8B shows the nucleotide sequence of the Plasmodium falciparum-B linker regions of pAP-225 (SEQ ID NO.14);

Figure 8C shows the subcloning of the Plasmodium falciparum-B linker variant into a baculovirus transfer vector;

Figure 8D shows the DNA sequence of the pAP-226 insert containing ricin and the Plasmodium falciparum-B linker (SEQ ID NO.15);

Figure 9A summarizes the cloning strategy used to generate the pAP-227 construct;

Figure 9B shows the nucleotide sequence of the Plasmodium falciparum-C linker regions of pAP-227 (SEQ ID NO.16);

Figure 9C shows the subcloning of the Plasmodium falciparum-C linker variant into a baculovirus transfer vector;

Figure 9D shows the DNA sequence of the pAP-228 insert containing ricin and the Plasmodium falciparum-C linker (SEQ ID NO.17);

Figure 10A summarizes the cloning strategy used to generate the pAP-229 construct;

Figure 10B shows the nucleotide sequence of the Plasmodium falciparum-D linker regions of pAP-229 (SEQ ID NO.18);

Figure 10C shows the subcloning of the Plasmodium falciparum-D linker variant into a baculovirus transfer vector;

Figure 10D shows the DNA sequence of the pAP-230 insert containing ricin and the Plasmodium falciparum-D linker (SEQ ID NO.19);

Figure 11A summarizes the cloning strategy used to generate the pAP-231 construct;

Figure 11B shows the nucleotide sequence of the Plasmodium falciparum-E linker regions of pAP-231 (SEQ ID NO.20);

Figure 11C shows the subcloning of the Plasmodium falciparum-E linker variant into a baculovirus transfer vector;

Figure 11D shows the DNA sequence of the pAP-232 insert containing ricin and the Plasmodium falciparum-E linker (SEQ ID NO.21);

Figure 12A summarizes the cloning strategy used to generate the pAP-233 construct;

Figure 12B shows the nucleotide sequence of the HSV-A linker regions of pAP-233 (SEQ ID NO.22);

Figure 12C shows the subcloning of the HSV-A linker variant into a baculovirus transfer vector;

Figure 12D shows the DNA sequence of the pAP-234 insert containing ricin and the HSV-A linker (SEQ ID NO.23);

Figure 13A summarizes the cloning strategy used to generate the pAP-235 construct;

Figure 13B shows the nucleotide sequence of the HSV-B linker regions of pAP-235 (SEQ ID NO.24);

Figure 13C shows the subcloning of the HSV-B linker variant into a baculovirus transfer vector;

Figure 13D shows the DNA sequence of the pAP-236 insert containing ricin and the HSV-B linker (SEQ ID NO.25);

Figure 14A summarizes the cloning strategy used to generate the pAP-237 construct;

Figure 14B shows the nucleotide sequence of the VZV-A linker regions of pAP-237 (SEQ ID NO.26);

Figure 14C shows the subcloning of the VZV-A linker variant into a baculovirus transfer vector;

Figure 14D shows the DNA sequence of the pAP-238 insert containing ricin and the VZV-A linker (SEQ ID NO.27);

Figure 15A summarizes the cloning strategy used to generate the pAP-239 construct;

Figure 15B shows the nucleotide sequence of the VZV-B linker regions of pAP-239 (SEQ ID NO.28);

Figure 15C shows the subcloning of the VZV-B linker variant into a baculovirus transfer vector;

Figure 15D shows the DNA sequence of the pAP-240 insert containing ricin and the VZV-B linker (SEQ ID NO.29);

Figure 16A summarizes the cloning strategy used to generate the pAP-241 construct;

Figure 16B shows the nucleotide sequence of the EBV-A linker regions of pAP-241 (SEQ ID NO.30);

Figure 16C shows the subcloning of the EBV-A linker variant into a baculovirus transfer vector;

Figure 16D shows the DNA sequence of the pAP-242 insert containing ricin and the EBV-A linker (SEQ ID NO.31);

Figure 17A summarizes the cloning strategy used to generate the pAP-243 construct;

Figure 17B shows the nucleotide sequence of the EBV-B linker regions of pAP-243 (SEQ ID NO.32);

Figure 17C shows the subcloning of the EBV-B linker variant into a baculovirus transfer vector;

Figure 17D shows the DNA sequence of the pAP-244 insert containing ricin and the EBV-B linker (SEQ ID NO.33);

Figure 18A summarizes the cloning strategy used to generate the pAP-245 construct;

Figure 18B shows the nucleotide sequence of the CMV-A linker regions of pAP-245 (SEQ ID NO.34);

Figure 18C shows the subcloning of the CMV-A linker variant into a baculovirus transfer vector;

Figure 18D shows the DNA sequence of the pAP-246 insert containing ricin and the CMV-A linker (SEQ ID NO.35);

Figure 19A summarizes the cloning strategy used to generate the pAP-247 construct;

Figure 19B shows the nucleotide sequence of the CMV-B linker regions of pAP-247 (SEQ ID NO.36);

Figure 19C shows the subcloning of the CMV-B linker variant into a baculovirus transfer vector;

Figure 19D shows the DNA sequence of the pAP-248 insert containing ricin and the CMV-B linker (SEQ ID NO.37);

Figure 20A summarizes the cloning strategy used to generate the pAP-249 construct;

Figure 20B shows the nucleotide sequence of the HHV-6 linker regions of pAP-249 (SEQ ID NO.38);

Figure 20C shows the subcloning of the HHV-6 linker variant into a baculovirus transfer vector;

Figure 20D shows the DNA sequence of the pAP-250 insert containing ricin and the HHV-6 linker (SEQ ID NO.39);

Figure 21 shows the amino acid sequences of the wild type ricin linker and cancer protease-sensitive amino acid linkers contained in pAP-213 to pAP-222 and linkers pAP-241 to pAP-244 (SEQ ID NOS.127 & 40-46);

Figure 22A summarizes the cloning strategy used to generate the pAP-253 construct;

Figure 22B shows the nucleotide sequence of the ILV linker regions of pAP-253 (SEQ ID NO.47);

Figure 22C shows the subcloning of the ILV linker variant into a baculovirus transfer vector;

Figure 22D shows the DNA sequence of the pAP-254 insert containing ricin and the ILV linker (SEQ ID NO.48);

Figure 23A summarizes the cloning strategy used to generate the pAP-257 construct;

Figure 23B shows the nucleotide sequence of the HAV-A linker regions of pAP-257 (SEQ ID NO.49);

Figure 23C shows the subcloning of the HAV-A linker variant into a baculovirus transfer vector;

Figure 23D shows the DNA sequence of the pAP-258 insert containing ricin and the HAV-A linker (SEQ ID NO.50);

Figure 24A summarizes the cloning strategy used to generate the pAP-255 construct;

Figure 24B shows the nucleotide sequence of the HAV-B linker regions of pAP-255 (SEQ ID NO.51);

Figure 24C shows the subcloning of the HAV-B linker variant into a baculovirus transfer vector;

Figure 24D shows the DNA sequence of the pAP-256 insert containing ricin and the HAV-B linker (SEQ ID NO.52);

Figure 25A summarizes the cloning strategy used to generate the pAP-259 construct;

Figure 25B shows the nucleotide sequence of the CAN linker regions of pAP-259 (SEQ ID NO.53);

Figure 25C shows the subcloning of the CAN linker variant into a baculovirus transfer vector;

Figure 25D shows the DNA sequence of the pAP-260 insert containing ricin and the CAN linker (SEQ ID NO.54);

Figure 26 shows the amino acid sequences of the wild type ricin linker and *Plasmodium falciparum* protease-sensitive amino acid linkers contained in linkers pAP-223 to pAP-232 (SEQ ID NOS.127 & 55-59);

Figure 27 shows the amino acid sequences of the wild type ricin linker and the viral protease-sensitive amino acid linkers contained in pAP-233 to pAP-240, pAP-245-pAP-248, pAP-253 to pAP-258 (SEQ ID NOS.127, 63-64, 60-62, 65-69);

Figure 28 shows the amino acid sequences of the wild type ricin linker and the *Candida* aspartic protease-sensitive amino acid linker contained in pAP-259 to pAP-264 (SEQ ID NOS.127, 70-72);

Figure 29 describes an alternative mutagenesis and subcloning strategy to provide a baculovirus transfer vector containing the ricin-like toxin variant gene; and

Figure 30A summarizes the cloning strategy used to generate the pAP-262 construct;

Figure 30B shows the nucleotide sequence of the HCV-A linker region of pAP-262 (SEQ ID NO.73);

Figure 30C shows the DNA sequence of the pAP-262 insert (SEQ ID NO.74);

Figure 30D shows the amino acid sequence comparison of mutant preproricin linker region HCV-A to wild type (SEQ ID NOS.127, 75);

Figure 31A summarizes the cloning strategy used to generate the pAP-264 construct;

Figure 31B shows the nucleotide sequence of the HCV-B linker region of pAP-264 (SEQ ID NO.76);

Figure 31C shows the DNA sequence of the pAP-264 insert (SEQ ID NO.77);

Figure 31D shows the amino acid sequence comparison of mutant preproricin linker region HCV-B to wild type (SEQ ID NOS.127, 78);

Figure 32A summarizes the cloning strategy used to generate the pAP-266 construct;

Figure 32B shows the nucleotide sequence of the HCV-C linker region of pAP-266 (SEQ ID NO.79);

Figure 32C shows the DNA sequence of the pAP-266 insert (SEQ ID NO.80);

Figure 32D shows the amino acid sequence comparison of mutant preproricin linker region HCV-C to wild type (SEQ ID NOS.127, 81);

Figure 33A summarizes the cloning strategy used to generate the pAP-268 construct;

Figure 33B shows the nucleotide sequence of the HCV-D linker region of pAP-268 (SEQ ID NO.82);

Figure 33C shows the DNA sequence of the pAP-268 insert (SEQ ID NO.83);

Figure 33D shows the amino acid sequence comparison of mutant preproricin linker region HCV-D to wild type (SEQ ID NOS.127, 84);

Figure 34A summarizes the cloning strategy used to generate the pAP-270 construct;

Figure 34B shows the nucleotide sequence of the MMP-2 linker region of pAP-270 (SEQ ID NO.85);

Figure 34C shows the DNA sequence of the pAP-270 insert (SEQ ID NO.86);

Figure 34D shows the amino acid sequence comparison of mutant preproricin linker region of MMP-2 to wild type (SEQ ID NOS.127, 87);

Figure 35A summarizes the cloning strategy used to generate the pAP-272 construct;

Figure 35B shows the nucleotide sequence of the Cathepsin B (Site 2) linker region of pAP-272 (SEQ ID NO.88);

Figure 35C shows the DNA sequence of the pAP-272 insert (SEQ ID NO.89);

Figure 35D shows the amino acid sequence comparison of mutant preproricin linker region of Cathepsin B (Site 2) to wild type (SEQ ID NO.90);

Figure 36A summarizes the cloning strategy used to generate the pAP-274 construct;

Figure 36B shows the nucleotide sequence of the Cathepsin L linker region of pAP-274 (SEQ ID NO.91);

Figure 36C shows the DNA sequence of the pAP-274 insert (SEQ ID NO.92);

Figure 36D shows the amino acid sequence comparison of mutant preproricin linker region of Cathepsin L to wild type (SEQ ID NOS.127, 93);

Figure 37A summarizes the cloning strategy used to generate the pAP-276 construct;

Figure 37B shows the nucleotide sequence of the Cathepsin D linker region of pAP-276 (SEQ ID NO.94);

Figure 37C shows the DNA sequence of the pAP-276 insert (SEQ ID NO.95);

Figure 37D shows the amino acid sequence comparison of mutant preproricin linker region of Cathepsin D to wild type (SEQ ID NOS.127, 96);

Figure 38A summarizes the cloning strategy used to generate the pAP-278 construct;

Figure 38B shows the nucleotide sequence of the MMP-1 linker region of pAP-278 (SEQ ID NO.97);

Figure 38C shows the DNA sequence of the pAP-278 insert (SEQ ID NO.98);

Figure 38D shows the amino acid sequence comparison of mutant preproricin linker region of MMP-1 to wild type (SEQ ID NOS.127, 99);

Figure 39A summarizes the cloning strategy used to generate the pAP-280 construct;

Figure 39B shows the nucleotide sequence of the Urokinase Type Plasminogen Activator linker region of pAP-280 (SEQ ID NO.100);

Figure 39C shows the DNA sequence of the pAP-280 insert (SEQ ID NO.101);

Figure 39D shows the amino acid sequence comparison of mutant preproricin linker region of Urokinase-Type Plasminogen Activator to wild type (SEQ ID NO.102);

Figure 40A summarizes the cloning strategy used to generate the pAP-282 construct;

Figure 40B shows the nucleotide sequence of the MT-MMP linker region of pAP-282 (SEQ ID NO.103);

Figure 40C shows the DNA sequence of the pAP-282 insert (SEQ ID NO.104);

Figure 40D shows the amino acid sequence comparison of mutant preproricin linker region of MT-MMP to wild type (SEQ ID NOS.127, 105);

Figure 41A summarizes the cloning strategy used to generate the pAP-284 construct;

Figure 41B shows the nucleotide sequence of the MMP-11 linker region of pAP-284 (SEQ ID NO.106);

Figure 41C shows the DNA sequence of the pAP-284 insert (SEQ ID NO.107);

Figure 41D shows the amino acid sequence comparison of mutant preproricin linker region of MMP-11 to wild type (SEQ ID NOS.127, 108);

Figure 42A summarizes the cloning strategy used to generate the pAP-286 construct;

Figure 42B shows the nucleotide sequence of the MMP-13 linker region of pAP-286 (SEQ ID NO.109);

Figure 42C shows the DNA sequence of the pAP-286 insert (SEQ ID NO.110);

Figure 42D shows the amino acid sequence comparison of mutant preproricin linker region of MMP-13 to wild type (SEQ ID NOS.127, 111);

Figure 43A summarizes the cloning strategy used to generate the pAP-288 construct;

Figure 43B shows the nucleotide sequence of the Tissue type Plasminogen Activator linker region of pAP-288 (SEQ ID NO.112);

Figure 43C shows the DNA sequence of the pAP-288 insert (SEQ ID NO.113);

Figure 43D shows the amino acid sequence comparison of mutant preproricin linker region of Tissue-type Plasminogen Activator to wild type (SEQ ID NOS.127, 114);

Figure 44A summarizes the cloning strategy used to generate the pAP-290 construct;

Figure 44B shows the nucleotide sequence of the human Prostate-Specific Antigen linker region of pAP-290 (SEQ ID NO.115);

Figure 44C shows the DNA sequence of the pAP-290 insert (SEQ ID NO.116);

Figure 44D shows the amino acid sequence comparison of mutant preproricin linker region of the human Prostate-Specific Antigen to wild type (SEQ ID NOS.127, 117);

Figure 45A summarizes the cloning strategy used to generate the pAP-292 construct;

Figure 45B shows the nucleotide sequence of the kallikrein linker region of pAP-292 (SEQ ID NO.118);

Figure 45C shows the DNA sequence of the pAP-292 insert (SEQ ID NO.119);

Figure 45D shows the amino acid sequence comparison of mutant preproricin linker region of the kallikrein to wild type (SEQ ID NOS.127, 120);

Figure 46A summarizes the cloning strategy used to generate the pAP-294 construct;

Figure 46B shows the nucleotide sequence of the neutrophil elastase linker region of pAP-294 (SEQ ID NO.121);

Figure 46C shows the DNA sequence of the pAP-294 insert (SEQ ID NO.122);

Figure 46D shows the amino acid sequence comparison of mutant preproricin linker region of neutrophil elastase to wild type (SEQ ID NOS.127, 123);

Figure 47A summarizes the cloning strategy used to generate the pAP-296 construct;

Figure 47B shows the nucleotide sequence of the calpain linker region of pAP-296 (SEQ ID NO.124);

Figure 47C shows the DNA sequence of the pAP-296 insert (SEQ ID NO.125);

Figure 47D shows the amino acid sequence comparison of mutant preproricin linker region of calpain to wild type (SEQ ID NOS.127, 126);--

Please replace the paragraph beginning at page 25, line 20, with the following rewritten paragraph:

--Figure 52 is a blot showing cleavage of pAP-248 with Human Cytomegalovirus (HCMV).--

Please replace the paragraph beginning at page 45, line 9, with the following rewritten paragraph:

--Recombinant expression vectors can be introduced into host cells to produce a transformant host cell. The term "transformant host cell" is intended to include prokaryotic and eukaryotic cells which have been transformed or transfected with a

recombinant expression vector of the invention. The terms "transformed with", "transfected with", "transformation" and "transfection" are intended to encompass introduction of nucleic acid (e.g. a vector) into a cell by one of many possible techniques known in the art. Prokaryotic cells can be transformed with nucleic acid by, for example, electroporation or calcium-chloride mediated transformation. Nucleic acid can be introduced into mammalian cells via conventional techniques such as calcium phosphate or calcium chloride co-precipitation, diethylaminoethyl-dextran (DEAE-dextran) mediated transfection, lipofectin, electroporation or microinjection. Suitable methods for transforming and transfecting host cells can be found in Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press (1989)), and other laboratory textbooks.--

Please replace the paragraph beginning at page 57, line 18, with the following rewritten paragraph:

--Oligonucleotides, corresponding to the extreme 5' and 3' ends of the preproricin gene were synthesized and used to polymerase chain reaction (PCR) amplify the gene. Using the cDNA sequence for preproricin (Lamb et al., Eur. J. Biochem., 145:266-270, 1985), several oligonucleotide primers were designed to flank the start and stop codons of the preproricin open reading frame. The oligonucleotides were synthesized using an Applied Biosystems Model 392 DNA/RNA Synthesizer. First strand cDNA synthesis was primed using the oligonucleotide Ricin1729C (Table 1). Three micrograms of total RNA was used as a template for oligo Ricin1729C primed synthesis of cDNA using Superscript II Reverse Transcriptase (BRL) following the manufacturer's protocol.--

Please replace the paragraph beginning at page 59, line 10, with the following rewritten paragraph:

--pAP144 cut with EcoRI was used as target for PCR pairs employing the Ricin109-Eco oligonucleotide (Ricin-109Eco primer: 5 GGAGGAATCCGGAGATGAAACCGGGAGGAAATACTATTGTAAT-3 (SEQ ID No. 141)) and a mutagenic primer for the 5' half of the linker as well as the Ricin1729PstI primer (Ricin1729-PstI: 5 GTAGGCGCTGCAGATAACTTGCTGTCCTTTCAG-3 (SEQ

ID No. 142)) and a mutagenic primer for the 3' half of the linker. The cycling conditions used for the PCRs were 98 ~~degrees~~°C for 2 min.; 98°C 1 min., 52°C 1 min., 72°C 1 min. 15 sec. (30 cycles); 72 ~~degrees~~°C 10min.; 4 ~~degrees~~°C soak. The PCR products were then digested by EcoRI and PstI respectively, electrophoresed on an agarose gel, and the bands purified by via glass wool spin columns. Triple ligations comprising the PCR product pairs (corresponding halves of the new linker) and pVL1393 vector digested with EcoRI and PstI were carried out. Recombinant clones were identified by restriction digests of plasmid miniprep DNA and the altered linkers confirmed by DNA sequencing. See Figure 45 as an example of the cloning strategy. Recombinant clones were identified by restriction digests of plasmid miniprep DNA and the altered linkers confirmed by DNA sequencing. Note that since all altered linker variants were cloned directly into the pVL1393 vector odd-numbered pAPs were no longer required or produced.--

Please replace the paragraph beginning at page 60, line 27, with the following rewritten paragraph:

--Protein samples were harvested three days post transfection. The cells were removed by centrifuging the media at 8288 g for ten minutes using a GS3 (Sorvall) centrifuge rotor. The supernatant was further clarified by centrifuging at 25400 g using a SLA-1500 rotor (Sorvall) for 45 minutes. Protease inhibitor phenylmethylsulfonyl fluoride (Sigma) was slowly added to a final concentration of 1mM. The samples were further prepared by adding lactose to a concentration of 20 mM (not including the previous lactose contained in the expression medium). The samples were concentrated to 700 mL using a Prep/Scale-TFF Cartridge (2.5ft, 10K regenerated cellulose (Millipore)) and a Masterflex pump. The samples were then dialysed for 2 days in 1X Column Buffer (50 mM Tris, 100 mM NaCl, 0.02% ~~NaN3~~ NaN_3, pH 7.5) using dialysis tubing (10 K MWCO, 32 mm flat width (Spectra/Por)). Subsequently, the samples were clarified by ~~centri-fuging~~ centrifuging at 25400 g using a SLA-1500 rotor (Sorvall) for 45 minutes.--

Please replace the paragraph beginning at page 61, line 7, with the following rewritten paragraph:

--Following centrifugation, the samples were degassed and applied at 4 ~~degrees~~° C to a XK26/20 (Pharmacia) column (attached to a Pharmacia peristaltic pump, Pharmacia Single-path Monitor UV-1 Control and Optical Units, and Bromma LKB 2210 2-Channel Recorder) containing 20 mL of α~~a~~-Lactose Agarose Resin (Sigma). The column was washed for 3 hours with 1X Column buffer. Elution of pro-ricin variant was performed by eluting with buffer (1X Column buffer (0.1% NaN3), 100 mM Lactose) until the baseline was again restored. The samples were concentrated using an Amicon 8050 concentrator (Amicon) with a YM10 76 mm membrane, utilizing argon gas to pressurize the chamber. The samples were further concentrated in Centricon 10 (Millipore) concentrators according to manufacturer's specifications.--

Please replace the paragraph beginning at page 61, line 20, with the following rewritten paragraph:

--In order to purify the pro-ricin variant from processed material produced during fermentation, the protein was applied to a SUPERDEX 75 (16/60) column and SUPERDEX 200 (16/60) column (Pharmacia) connected in series equilibrated with 50 mM Tris, 100mM NaCl, pH 7.5 containing 100 mM Lactose and 0.1% β-mercaptoethanol (βME). The flow rate of the column was 0.15 mL/min and fractions were collected every 25 minutes. The ~~UV~~ ultraviolet (280 nm) trace was used to determine the approximate location of the purified pAP-protein and thus determine the samples for Western analysis.--

Please replace the paragraph beginning at page 62, line 6, with the following rewritten paragraph:

--Following electrophoresis gels were equilibrated in transfer buffer (48 mM Tris, 39 mM glycine, 0.0375% SDS, and 20% Methanol) for a few minutes. Polyvinyl difluoride (PVDF) Biorad membrane was presoaked for one minute in 100% methanol, rinsed in ~~ddH2O~~ deionized distilled water and two minutes in transfer buffer. Whatman

paper was soaked briefly in transfer buffer. Five pieces of Whatman paper, membrane, gel, and another five pieces of Whatman paper were arranged on the bottom cathode (anode) of the Pharmacia Novablot transfer apparatus (Pharmacia). Transfer was for one hour at constant current (2 mA/cm2).--

Please replace the paragraph beginning at page 72, line 1, with the following rewritten paragraph:

--Affinity-purified mutant proricin mutants which were previously digested with the disease-specific protease, were reduced with 5% 2-mercaptoethanol then diluted to 100ng, 14.2ng,_2.0ng,_291pg, and 41.7pg with 1 X ENDO buffer_(25mM Tris pH 7.6, 25mM KCl, 5mM $MgCl_2$) and incubated with rabbit reticulocyte lysate, untreated (Promega) for 30minutes at 30{°C. To compare the digested with the undigested proricin variant, the proricin in digestion buffer (according to the specific digestion protocol) was treated in the same manner as the digested sample. As a positive and negative control, 10ng of ricin A chain and 1 X ENDO buffer consecutively, was incubated with rabbit reticulocyte lysate, untreated, for 30 min at 30°C.--

Please replace the paragraph beginning at page 72, line 13, with the following rewritten paragraph:

--Total RNA was then extracted from reticulocyte lysate translation mixtures with Trizol reagent (Gibco-BRL) as per manufacturer's instructions. The RNA was incubated with 80ul of 1M aniline (distilled) with 2.8M acetic acid for 3 min at 60{°C in the dark. Ethanol-precipitated RNA samples were dissolved in 20ul of 50% formamide, 0.1X E buffer (3.6mM Tris, 3mM NaH2PO4, 0.2mM EDTA), and 0.05% xylene cyanol. 10ul of this was heated to 70{°C for 2 minutes, loaded and electrophoresed in 1.2% agarose, 0.1X E buffer, and 50% formamide gel with RNA running buffer (0.1 X E buffer, 0.2% SDS).--

Please replace the paragraph beginning at page 73, line 12, with the following rewritten paragraph:

--After washing with 1XPBS (0.137 M NaCl, 2.68 mM KCl, 8.10 mM Na_2HPO_4, 1.47 mM KH_2PO_4), cells in log phase growth were removed from plates with 1X trypsin/EDTA (Gibco/BRL). The cells were centrifuged at 1100 rpm for 3 min, resuspended in Dulbecco's Modified Eagle Medium containing 10%FBS and 1X pen/strep, and then counted using a haemocytometer. They were adjusted to a concentration of 5 X 10^4 cells•ml^{-1}. One hundred microliters per well of cells was added to wells 2B - 2G through to wells 9B - 9G of a Falcon 96 well tissue culture plate. A separate 96 well tissue culture plate was used for each sample of Ricin or Ricin variant. The plates were incubated at 37±°C with 5% CO_2 for 24 hours.--

Please replace the paragraph beginning at page 74, line 1, with the following rewritten paragraph:

--Columns 2 to 9 were labeled: control, 1000 ng•ml^{-1}, 100 ng•ml^{-1}, 10 ng•ml^{-1}, 1 ng•ml^{-1}, 0.1 ng•ml^{-1}, 0.01 ng•ml^{-1}, 0.001 ng•ml^{-1} consecutively. The media was removed from all the sample wells with a multichannel pipettor. For each plate of variant and toxin, 50µl of media was added to wells 2B to 2G as the control, and 50µl of each sample dilution was added to the corresponding columns. For the pAP220 + MMP-9 data, the plates were incubated for one hour at 37±°C with 5% CO2, then washed once and replaced with media, then incubated for 48 hours at 37±°C with 5% CO_2. For the pAP 214 + Cathepsin B data, the toxin was left on the plates and incubated for 24 hours at 37±°C with 5% CO_2, then 50 µl of media was added to the wells with the toxin and incubated for another 24 hours at 37±°C with 5% CO_2.--

Please replace the paragraph beginning at page 74, line 14, with the following rewritten paragraph:

--The whole amount of media (and/or toxin) was removed from each well with a multichannel pipettor, and replaced with 100 µl of the substrate mixture (Promega Cell Titer 96 Aqueous Non-Radioactive Cell Proliferation Assay Kit). The plates were incubated at 37±°C with 5% CO_2 for 2 to 4 hours, and subsequently read with a

Spectramax 340 96 well plate reader at 490nm. The IC_{50} values were calculated using the GRAFIT software program.--

Please replace the paragraph beginning at page 75, line 1, with the following rewritten paragraph:

--After washing with 1XPBS (~~1.37M~~ 0.137M NaCl, 26.8mM KCl, 81mM Na2HPO4, 14.7mM KH_2PO_4), cells in log phase growth were removed from plates with 1X trypsin/EDTA (Gibco/BRL). The cells were centrifuged at 1100 rpm for 3 min, resuspended in media containing 10%FBS and 1X pen/strep (media used depended on the cell line being tested), and then counted using a haemocytometer. They were adjusted to a concentration of 5 X 10^4 cells•ml^{-1} (faster growing cell lines were adjusted to 2 X10^4 cells•ml^{-1}). One hundred microliters per well of cells was added to wells 2B - 2G through to wells 9B - 9G of a Falcon 96 well tissue culture plate. A separate 96 well tissue culture plate was used for each sample of Ricin or Ricin variant. The plates were incubated at 37±°C with 5% CO_2 for 24 hours.--

Please replace the paragraph beginning at page 75, line 23, with the following rewritten paragraph:

--Columns 2 to 9 were labeled: control, 0.001 ng•ml^{-1}, 0.01 ng•ml^{-1}, 0.1 ng•ml^{-1}, 1ng•ml^{-1}, 10 ng•ml^{-1}, 100 ng•ml^{-1}, 1000 ng•ml^{-1} consecutively. For each plate of variant and toxin, 50µl of media was added to wells 2B to 2G as the control, and 50µl of each sample dilution was added to the corresponding columns containing 100µl per well of cells (i.e. 50 µl of the 3000 ng•ml^{-1} dilution added to the wells B-G in column 9, labeled 1000 ng•ml^{-1}). The plates were incubated for 48 hours at 37±°C with 5% CO_2.--

Please replace the paragraph beginning at page 75, line 32, with the following rewritten paragraph:

--An amount of 140µl was removed from each well with a multichannel pipettor, and replaced with 100 µl of the substrate mixture (Promega Cell Titer 96 Aqueous Non-Radioactive Cell Proliferation Assay Kit). The plates were incubated at 37±°C with 5%

CO_2 for 2 to 4 hours, and subsequently read with a Spectramax 340 96 well plate reader at 490nm. The IC_{50} values were calculated using the GRAFIT software program.--

Please replace Table 1 on page 79 with the following amended Table 1:

TABLE 1

Table I - Sequence and Location of Oligonucleotide Primers

Name of Primer	Primer Sequence†	SEQ ID NO:	Corresponds to preproricin nucleotide numbers: (see Figures 8-10)
Ricin-109	5'-GGAGATGAAACCGGGAGGAAATACTATTGTAAT-3'	130	27 to 59
Ricin-99Eco	5'- GCGGAATTCCGGGAGGAAATACTATTGTAAT-3'	131	37 to 59
Ricin 267	5'- ACGGTTTATTTTAGTTGA -3'	132	300 to 317
Ricin486	5'- ACTTGCTGGTAATCTGAG -3'	133	519 to 536
Ricin725	5'- AGAATAGTTGGGGGAGAC -3'	134	758 to 775
Ricin937	5'- AATGCTGATGTTTGTATG - 3'	135	970 to 987
Ricin1151	5'- CGGGAGTCTATGTGATGA - 3'	136	1184 to 1201
Ricin1399	5'- GCAAATAGTGGACAAGTA - 3'	137	1432 to 1449
Ricin1627	5'- GGATTGGTGTTAGATGTG - 3'	138	1660 to 1677
Ricin1729C	5'- ATAACTTGCTGTCCTTTCA - 3'	139	1864 to 1846
Ricin1729C Xba	5'- CGCTCTAGATAACTTGCTGTCCTTTCA - 3'	140	1864 to 1846

† underlined sequences inserted for subcloning purposes and not included in final preproricin sequences